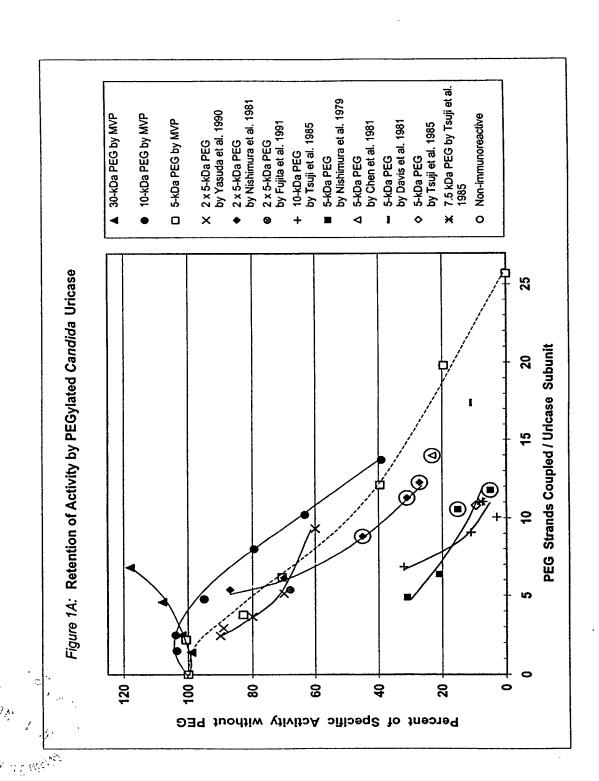
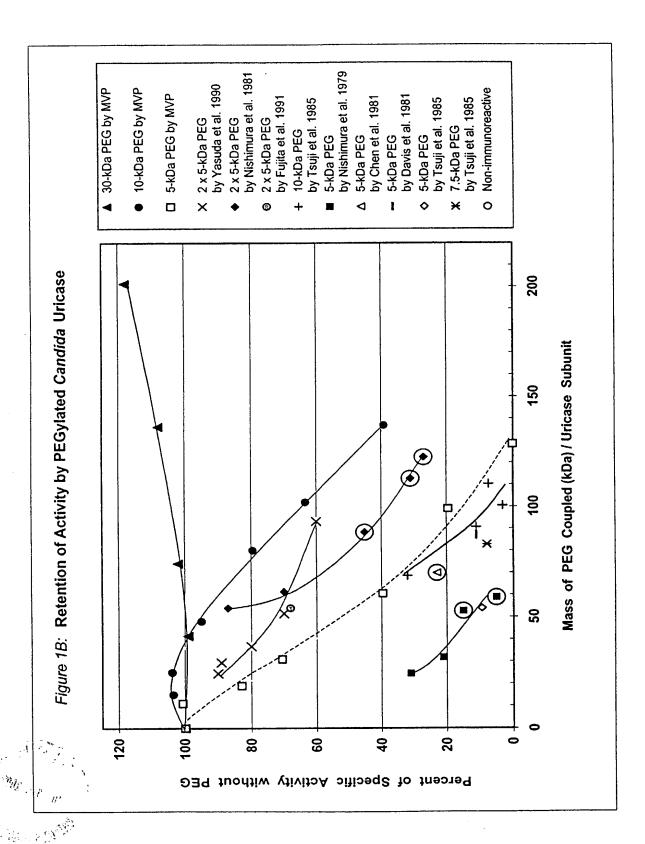
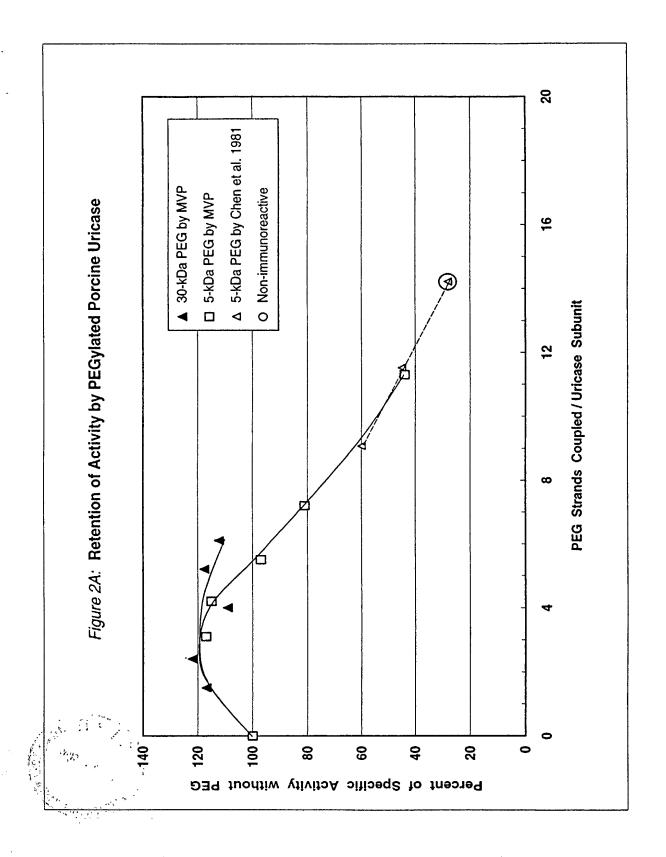
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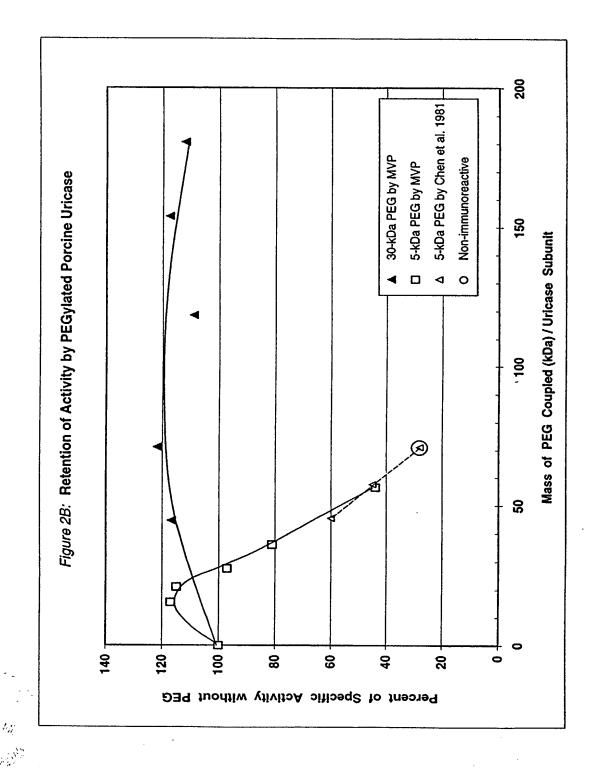


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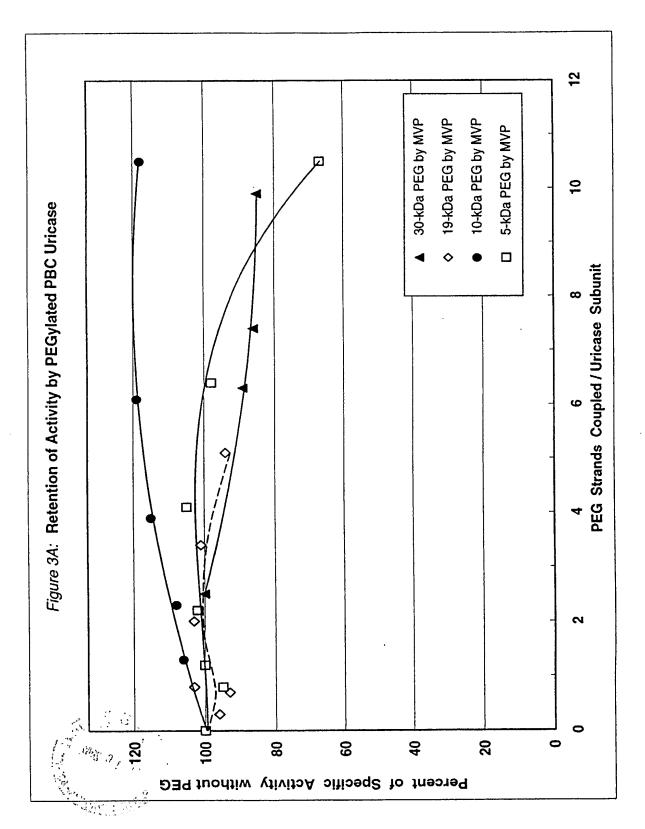
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Williams, et al.

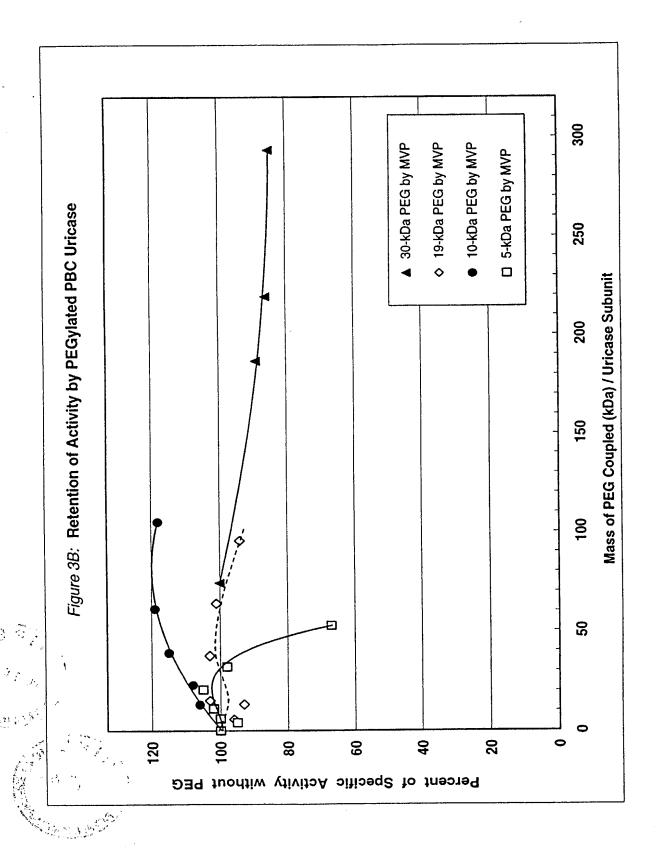
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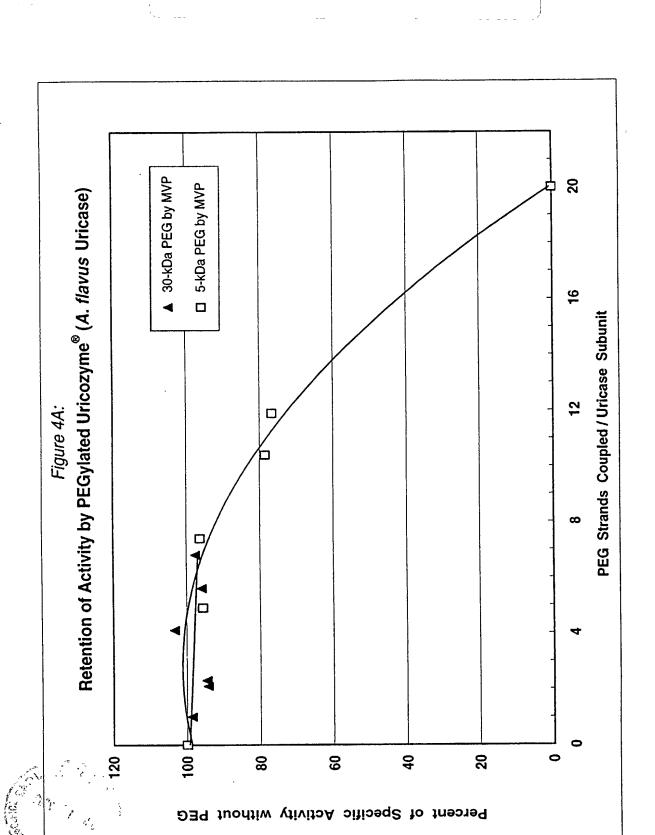


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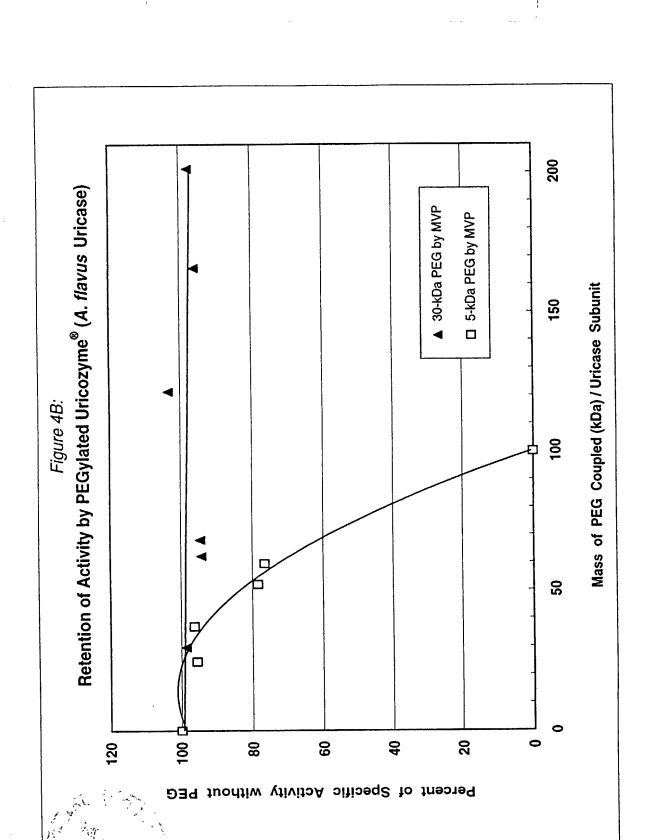
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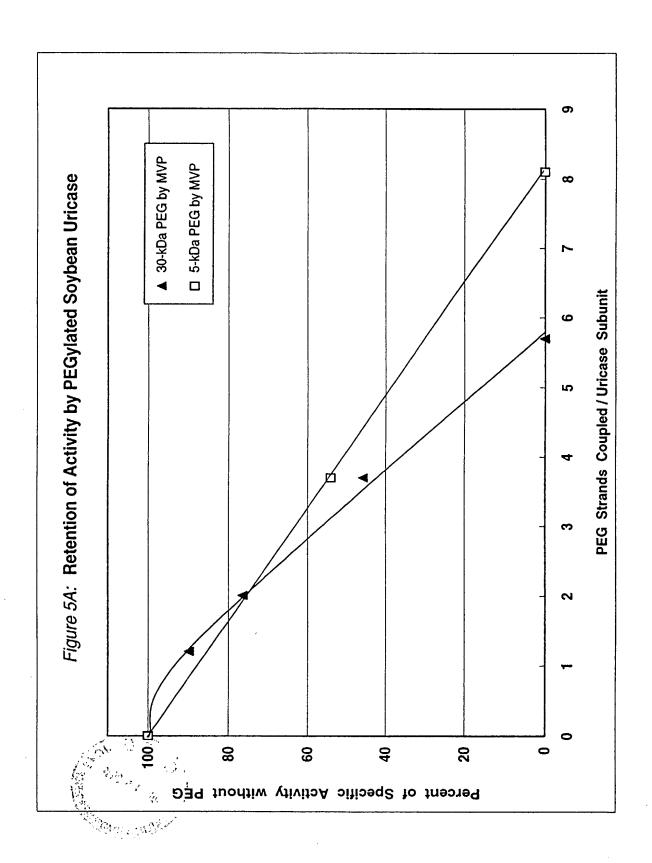
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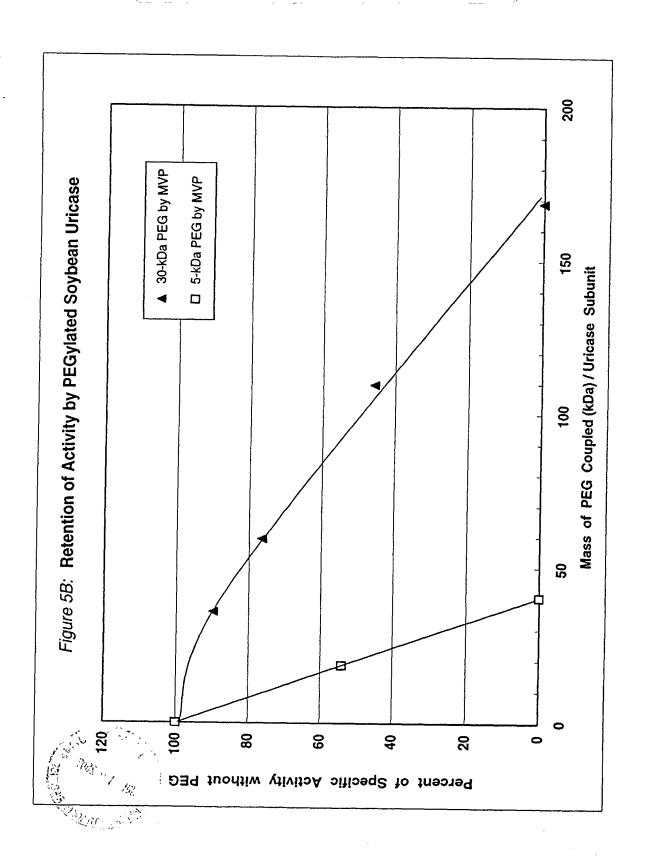


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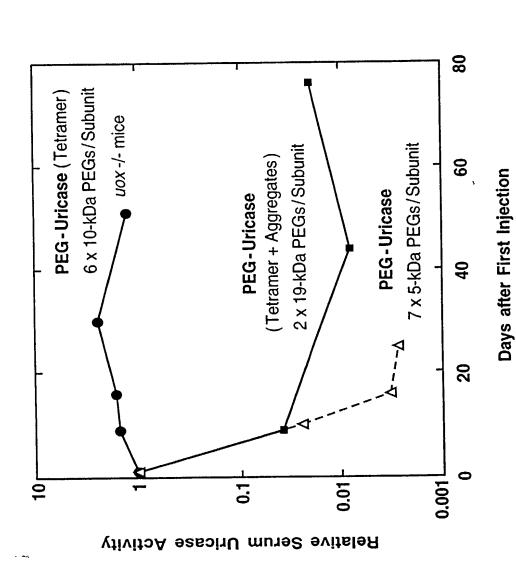
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Figure 6: Deduced amino acid sequences of Pig-Baboon Chimeric (PBC) uricase, PBC uricase that is truncated at the amino and carboxyl terminals (PBC-NT-CT) and Porcine uricase containing the mutations R291K and T301S (PKS Uricase) (SEQ ID NO:3), compared with the porcine sequence (SEQ ID NO: 1) and baboon sequence (SEQ ID NO: 2)

Porcine				
	MAHYRNDYKK NDEVEFVRTG	YGKDMIKVLH	IQRDGKYHSI	40
PBC	porcine sequence 1-225	\rightarrow		40
PBC-NT-CT	porcine sequence	: 1-219 →		34
PKS	porcine sequence 1-288			40
Baboon	MADYHNNYKK NDELEFVRTG	YGKDMVKVLH	IQRDGKYHSI	40
Porcine	KEVATSVQLT LSSKKDYLHG	DNSDVIPTDT	IKNTVNVLAK	80
PBC	porcine sequence $ ightarrow$			80
PBC-NT-CT	porcine sequence $ ightarrow$			74
PKS	porcine sequence →		T 1/2 1/27 1991 17 T 7 1/2	80
Baboon	KEVATSVQLT LSSKKDYLHG	DNSDIIPTDT	IKNTVHVLAK	80
Porcine PBC	FKGIKSIETF AVTICEHFLS	SFKHVIRAQV	YVEEVPWKRF	120
PBC-NT-CT	porcine sequence →			120 114
PKS	porcine sequence →			120
Baboon	porcine sequence → FKGIKSIEAF GVNICEYFLS	SFNHVIRAQV	YVEEIPWKRL	120
	~ ~~			
Porcine	EKNGVKHVHA FIYTPTGTHF	CEVEQIRNGP	PVIHSGIKDL	160
PBC	porcine sequence →			160
PBC-NT-CT	porcine sequence →			154
	porcine sequence \rightarrow			160
PKS	_			
PKS Baboon	EKNGVKHVHA FIHTPTGTHF	CEVEQ L R S GP	PVIHSGIKDL	160
Baboon Porcine	_	CEVEQLRSGP LPEVKDRCFA	PVIHSGIKDL TQVYCKWRYH	200
Baboon	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence →			
Baboon Porcine	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT			200
Baboon Porcine PBC	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence →			200
Baboon Porcine PBC PBC-NT-CT	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence → porcine sequence →			200 200 194
Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence → porcine sequence → kvlkttqsgf Egfikdqftt QGRDVDFEAT WDTVRSIVLQ	LPEVKDRCFA	TQVYCKWRYH	200 200 194 200 200 240
Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence porcine sequence kvlkttqsgf Egfikdqftt QGRDVDFEAT WDTVRSIVLQ porcine sequence	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE → ← bal	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY poon sequence	200 200 194 200 200 240 240
Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence → porcine sequence → KVLKTTQSGF EGFIKDQFTT QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE → ← bal	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY	200 200 194 200 200 240 240 234
Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT PKS	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence → porcine sequence → KVLKTTQSGF EGFIKDQFTT QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence porcine sequence porcine sequence porcine sequence	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE → ← bak → ← bak	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY coon sequence	200 200 194 200 200 240 240 234 240
Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT PKS Baboon	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence porcine sequence kvlkttqsgf Egfikdqftt QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence porcine sequence porcine sequence porcine sequence porcine sequence	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE → ← bal	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY poon sequence	200 200 194 200 200 240 240 234
Baboon Porcine PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence -> porcine sequence -> porcine sequence -> KVLKTTQSGF EGFIKDQFTT QGRDVDFEAT WDTVRSIVLQ porcine sequence POCRDVDFEAT WGTIRDLVLE DIQVLTLGQV PEIEDMEISL	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE → ← bak → ← bak	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY coon sequence	200 200 194 200 200 240 240 234 240 240 280
Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence -> porcine sequence -> kvlkttqsgf Egfikdqftt QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence porcine sequence porcine sequence porcine sequence porcine sequence -> QCRDVDFEAT WGTIRDLVLE DIQVLTLGQV PEIEDMEISL baboon sequence ->	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY coon sequence coon sequence	200 200 194 200 200 240 240 234 240 240 280 280
Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence -> porcine sequence -> kVLKTTQSGF EGFIKDQFTT QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence -> QCRDVDFEAT WGTIRDLVLE DIQVLTLGQV PEIEDMEISL baboon sequence -> baboon sequence ->	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY coon sequence coon sequence	200 200 194 200 240 240 234 240 240 280 280 274
Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT PKS	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence porcine sequence porcine sequence KVLKTTQSGF EGFIKDQFTT QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence porcine sequence porcine sequence porcine sequence QCRDVDFEAT WGTIRDLVLE DIQVLTLGQV PEIEDMEISL baboon sequence baboon sequence porcine sequence porcine sequence	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY coon sequence coon sequence YSPSVQKTLY SKMGLINKEE	200 200 194 200 240 240 234 240 240 280 274 280
Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT PKS Baboon Porcine PBC PBC-NT-CT PKS Baboon	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence porcine sequence kvlkttqsgf Egfikdqftt QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence baboon sequence porcine sequence baboon sequence porcine sequence baboon sequence porcine sequence DIQVLSLSRV PEIEDMEISL	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY coon sequence coon sequence	200 200 194 200 240 240 234 240 240 280 280 274
Baboon Porcine PBC PBC-NT-CT PKS Baboon	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence porcine sequence porcine sequence KVLKTTQSGF EGFIKDQFTT QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence porcine sequence porcine sequence QCRDVDFEAT WGTIRDLVLE DIQVLTLGQV PEIEDMEISL baboon sequence porcine sequence porcine sequence baboon sequence porcine sequence porcine sequence porcine sequence RITGTVKRKL	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY coon sequence coon sequence YSPSVQKTLY SKMGLINKEE	200 200 194 200 240 240 234 240 240 280 274 280
Baboon Porcine PBC PBC-NT-CT PKS Baboon	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence porcine sequence porcine sequence KVLKTTQSGF EGFIKDQFTT QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence porcine sequence porcine sequence QCRDVDFEAT WGTIRDLVLE DIQVLTLGQV PEIEDMEISL baboon sequence porcine sequence porcine sequence baboon sequence porcine sequence DIQVLSLSRV PEIEDMEISL VLLPLDNPYG RITGTVKRKL baboon sequence	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE → ← bak → ← bak KFAGPYDKGE PNIHYLNIDM PNIHYFNIDM TSRL 304 304	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY coon sequence coon sequence YSPSVQKTLY SKMGLINKEE	200 200 194 200 240 240 234 240 240 280 274 280
Baboon Porcine PBC PBC-NT-CT PKS Baboon	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence -> porcine sequence -> porcine sequence -> KVLKTTQSGF EGFIKDQFTT QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence porcine sequence porcine sequence -> QCRDVDFEAT WGTIRDLVLE DIQVLTLGQV PEIEDMEISL baboon sequence -> porcine sequence -> porcine sequence -> DIQVLSLSRV PEIEDMEISL VLLPLDNPYG RITGTVKRKL baboon sequence -> baboon sequence ->	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE → ← bak KFAGPYDKGE PNIHYLNIDM PNIHYFNIDM TSRL 304 304 295	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY coon sequence coon sequence YSPSVQKTLY SKMGLINKEE	200 200 194 200 240 240 234 240 240 280 274 280
Baboon Porcine PBC PBC-NT-CT PKS Baboon	EKNGVKHVHA FIHTPTGTHF KVLKTTQSGF EGFIKDQFTT porcine sequence porcine sequence porcine sequence KVLKTTQSGF EGFIKDQFTT QGRDVDFEAT WDTVRSIVLQ porcine sequence porcine sequence porcine sequence porcine sequence QCRDVDFEAT WGTIRDLVLE DIQVLTLGQV PEIEDMEISL baboon sequence porcine sequence porcine sequence baboon sequence porcine sequence DIQVLSLSRV PEIEDMEISL VLLPLDNPYG RITGTVKRKL baboon sequence	LPEVKDRCFA LPEVKDRCFA KFAGPYDKGE → ← bak → ← bak KFAGPYDKGE PNIHYLNIDM PNIHYFNIDM TSRL 304 304	TQVYCKWRYH TQVYCKWRYH YSPSVQKTLY coon sequence coon sequence YSPSVQKTLY SKMGLINKEE	200 200 194 200 240 240 234 240 240 280 274 280

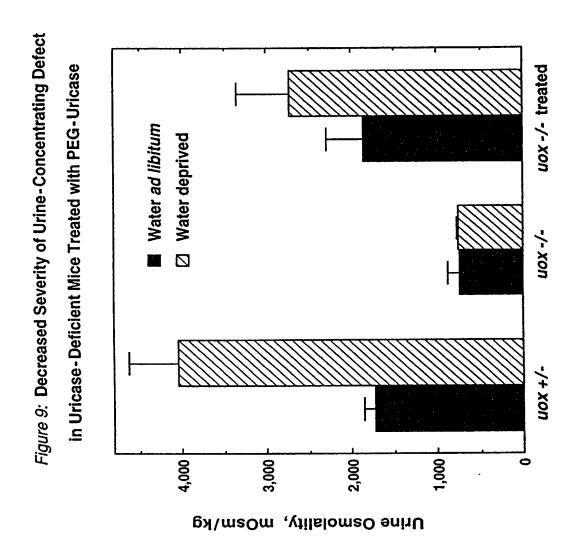
Figure 7: Serum Uricase Activity 24 Hours after Each PEG-Uricase Injection, Relative to the First Injection



Uric Acid in Urine, mg/10 mL Uric Acid in Serum, mg/dL Figure 8: Inverse Relationship between Serum PEG-Uricase Activity and Uric Acid Levels in the Serum and Urine of a Uricase-Deficient Mouse 6 160 Hours after First PEG-Uricase Injection 120 72 h 8 0.3 0.2 Serum Uricase Activity, IU/mL

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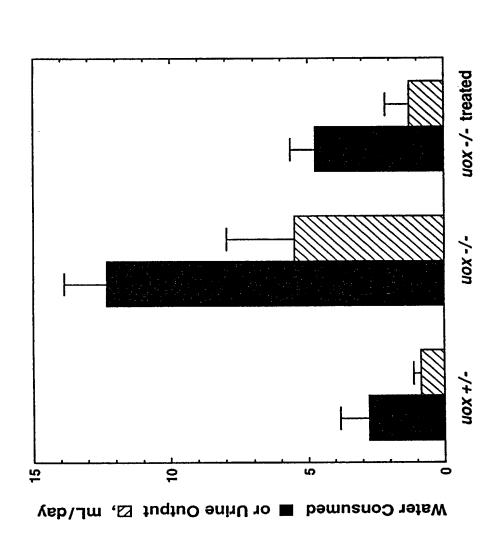
Williams, et al.
Atty Docket: MVIEWD.1A2DV1



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Figure 10: Decreased Severity of Nephrogenic Diabetes Insipidus in Uricase-Deficient Mice Treated with PEG-Uricase

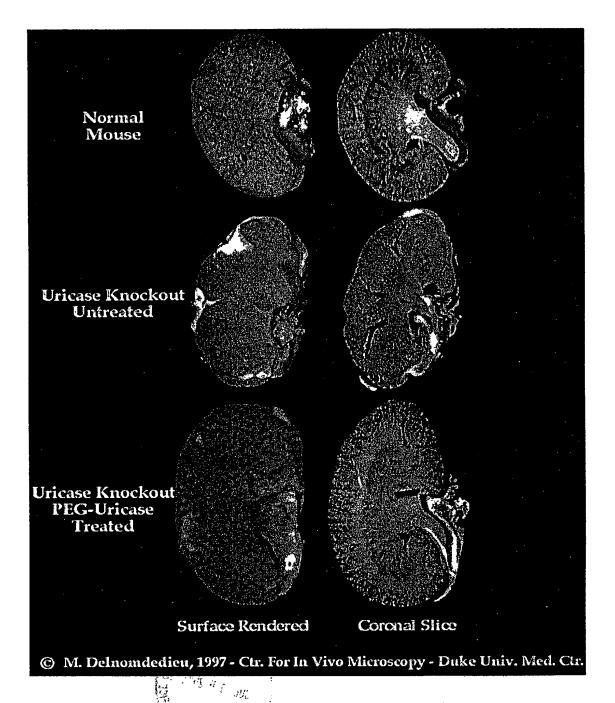




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Figure 11:

Decreased Severity of Uric Acid-Induced Nephropathy after Treatment with PEG-Uricase, as Visualized by Magnetic Resonance Microscopy



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Figure 12: Clearance from the Circulation of BALB/c Mice of PBC Uricase Tetramer and Octamer Coupled to 5-6 Strands of 10-kDa PEG/Subunit

